



Correspondence

Pain inhibits itch, but not in atopic dermatitis?



We read with great interest the article by Vakharia et al¹ in a recent issue of the *Annals*. The prospective study comprehensively addresses an overlooked aspect of the sensory symptoms associated with atopic dermatitis (AD). In 305 patients with AD, the study reported that pain was found in 42.7% and that 30.2% rated the cutaneous pain intensity as being moderate to very severe. This pain incidence is aligned with a previous study on the AD itch characteristics.² Vakharia et al¹ consistently found cutaneous pain to be associated with reduced quality of life (including: Patient-Oriented Eczema Measure, ItchyQOL, and Dermatology Life Quality Index) and to a lesser extent with objective disease severity. The patients with AD who experienced cutaneous pain with or without the occurrence of excoriations frequently used neuropathic pain-like descriptors, such as tingling, burning, and pinprick-like.

The high occurrence of burdensome cutaneous pain alongside itch in AD stimulates questions regarding the underlying mechanism(s). Pruriceptive and nociceptive signaling is conveyed by the same primary afferent cutaneous C-nociceptors, with the encoding features that allow sensory discrimination being unknown (various competing hypotheses have been proposed).³ Although certain itch provocations in healthy volunteers produce itch and concomitant mild cutaneous pain, homotopic pain generally inhibits itch and itch dysesthesias in the healthy somatosensory system.^{4,5} This is true, for example, for scratching, heat pain, chemical pain provocations, and even when the pain stimuli precede the itch provocations.^{6,7} Moreover, in hyperalgesic skin, commonly observed in and around areas of cutaneous pain, itch sensitivity is greatly diminished.^{4,5,8} The circuitry by which pain inhibits itch is well studied in rodents and relies on spinal interneurons receiving input from primary afferent nociceptors while inhibiting spinothalamic pruriceptive transmission.³

In healthy individuals, fairly mild noxious counterstimuli are sufficient to robustly inhibit evoked itch. However, patients with AD exhibit considerable somatosensory aberrations to cutaneous stimuli; they have significant pinprick hyperalgesia and sensitization to nonhistaminergic itch in lesional and nonlesional skin.⁹ On the basis of the study by Vakharia et al,¹ it is evident that severe pain and itch exist concomitantly in a significant proportion of patients with AD. This cannot be mimicked in healthy individuals and is difficult to explain without considering a maladaptive central processing of itch, leading to a blunting of normal pain-induced itch suppression. A previous preliminary psychophysical experiment found such reduced itch inhibition to noxious counterstimulation in patients with AD and thus supports this working hypothesis.¹⁰ In this context, it is necessary to explicitly ascertain whether the patients experi-

ence itch and pain simultaneously or more sequentially, ie, as itch bouts, resulting in scratching and thus subsequently causing pain (which then wanes as the sequence repeats itself).

Because the pleasure that patients with AD derive from scratching is highly intervariable,² it would be interesting to know whether the patients with AD experiencing pain correspond to those rating scratching as being unpleasurable and possibly experience less itch relief from it. Studies that use psychophysical paradigms designed to measure the itch-inhibitory efficacy of controlled noxious counterstimuli would help us understand the involved mechanism, and possibly the implications, of pain and itch cooccurrence in AD. Such further research is also required to elucidate potential treatment approaches for cutaneous pain in AD. If the concomitance of pain and itch is indeed a consequence of central pruriceptive disinhibition, then analgesics might relieve the pain while worsening the itch. Of note, most patients reported that they felt the pain was scratch inflicted, which was in part substantiated by higher pain intensity ratings in patients with excoriations. If the pain is predominantly scratch evoked, then successful antipruritic therapy should also indirectly alleviate the pain, which consequently underscores the importance of directing treatment toward successful itch alleviation. Like itch, pain should be routinely assessed in AD, chiefly because it negatively affects quality of life but also because it likely has mechanistic and perhaps therapeutic implications.

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Authors' response



We read the correspondence by Andersen et al¹ with great interest. They made a number of important comments on our study of skin pain in atopic dermatitis (AD)² that we would like to address. Severe pain and itch were found to exist concomitantly in a significant proportion of patients with AD. To clarify this point, we re-evaluated the data and found that most patients had some itch in the past 24 hours (98.4%). Interestingly, there were numerically lower rates of skin pain in those with vs without itch in the past 24 hours (46.2% vs 75.0%). This fits with the observation that pain generally inhibits itch as observed in healthy subjects. In contrast, 97.4% of patients who reported any skin pain also reported itch in the past 24 hours. There also was a modest correlation between itch and skin pain published in our study (Spearman $\rho = 0.43$).² Together, there appears to be a substantial proportion of patients with AD who experience itch and pain simultaneously. These results could certainly fit with the speculated mechanism of a maladaptive central inhibitory processing of itch leading to a blunting of normal pain-induced itch suppression.

Unfortunately, we did not explicitly ascertain whether the patients actually experienced itch and pain simultaneously or sequentially as itch bouts resulting in scratching and pain. However, we found that 16.8% of patients believed their skin pain was part of their itch and not at all related to scratching. Of course, patients might not recognize the connection of their scratching and skin pain. We further examined the group of patients with pain reportedly from itch and unrelated to scratching and found some

fascinating associations. Patients who reported their skin pain was related to itch alone had significantly lower Patient-Oriented Eczema Measure ($P = .01$ by Mann-Whitney U test) and self-reported global AD severity ($P = .006$), but no differences of Dermatology Life Quality Index, 5-Dimensions Itch Scale, Eczema Area and Severity Index, or Scoring Atopic Dermatitis. These results should be interpreted cautiously because of limited statistical power. Nevertheless, they suggest that even patients with mild AD can experience skin pain. In addition, they suggest that some patients experience itch and pain simultaneously.

We agree that skin pain is an important symptom with potential therapeutic implications. We hope further studies from our group and other research groups will shed light on the best treatment approaches for skin pain in AD.

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Baseline asthma burden, comorbidities, and biomarkers in omalizumab-treated patients in PROSPERO



We read with interest comments from Oppenheimer and Greenberger¹ highlighting the baseline findings of the PROSPERO

trial that describe a real-world population with moderate to severe asthma accompanied by multiple comorbidities, a substantial disease burden, and a heterogeneous biomarker profile who began a treatment regimen with omalizumab.² We agree with their conclusions that patients with severe asthma represent a challenging population and that multiple factors must be considered when evaluating patients as candidates for biologic therapies. Highlighting imperfections in some of the supporting data cited in the editorial is important.

Oppenheimer and Greenberger¹ refer to a pharmacoeconomic analysis conducted by Oba and Salzman³ to describe the economic impact of omalizumab. Notably, as reflected by their discussion, this model included only direct costs and did not account for important indirect costs associated with poorly controlled asthma that also impact its global economic burden, including presenteeism and

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